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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/527,587 | 02/21/2006 | William E. Beschorner | 000241.00003 | 1006 |

22907 7590 08/20/2007

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| EXAMINER | |
|---|---|
| SAJJADI, FEREYDOUN GHOTB | |
| **ART UNIT** | **PAPER NUMBER** |
| 1633 | |
| **MAIL DATE** | **DELIVERY MODE** |
| 08/20/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/527,587 | BESCHORNER ET AL. | |
| | Examiner | Art Unit | |
| | Fereydoun G. Sajjadi | 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *12 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) *6* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 7-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 March 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/14/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Applicant's response of June 12, 2007, to the Restriction Requirement dated May 15, 2007 has been entered. No claims were amended, cancelled or newly added. Claims 1-12 are pending in the application.

### *Election/Restrictions*

Applicants' election of Group II (claims 1-5 and 7-12), drawn to, a method of engrafting foreign cells within a fetal non-human animal, wherein said cells are derived from a different species, is acknowledged. Applicants' election for the species of mutated thymidine kinase, liver and artiodactyls, is further acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

As the restriction is still deemed proper, the requirement for restriction is maintained and hereby made FINAL. Claim 6 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed June 12, 2007.

Elected claims 1-5, 9 and 7-12 are under current examination.

### *Information Disclosure Statement*

The information disclosure statement filed 3/4/2005 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been fully considered, since several references were not present in the instant application. Applicant is required to provide copies of the missing references to be considered by the examiner.

***Objections to the Specification/Abstract***

The abstract of the disclosure does not commence on a separate sheet in accordance with 37 CFR 1.52(b)(4). A new abstract of the disclosure is required and must be presented on a separate sheet, apart from any other text.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 4, 5, 7 and 8 are rejected under 35 U.S.C. §102(e) as being anticipated by Wu et al. (U.S. Patent No.: 6,995,299; filed Aug. 15, 2001).

Wu et al. teach propagation of human hepatocytes (limitation of claim 8) in non-human animals, wherein said animals have chimeric livers, whereby some of substantially all of the hepatocytes present are human hepatocytes (Title and Abstract). The animal comprising human hepatocytes is preferably a fetus (column 5, line 5; limitation of claim 1). Thus teaching that the human foreign replacement cells are derived from a different species than the fetal non-human host (limitation of claim 7).

Wu et al. state: "Non-human animals which may serve as hosts according to the invention are preferably mammals, and include, but are not limited to, mice, hamsters, rats, rabbits, dogs, goats, sheep, pigs, cattle, etc. (thus include even-toed ungulates, or artiodactyls; limitation of claim 5). In particular non-limiting embodiments of the invention, the host animal is a transgenic animal carrying, as a transgene, a gene which, when expressed in hepatocytes, is directly or indirectly (i.e. via a metabolite) toxic to those cells. Examples of such genes are the urokinase gene which is directly toxic (Sandgren et al., 1991, Cell 66:245), and the Herpes simplex virus

("HSV") thymidine kinase gene ("HSV-TK"); which converts the drug gancyclovir into a toxic form and is therefore indirectly toxic" (columns 12 and 13, bridging).

In describing conditions favoring the proliferation of human hepatocytes, Wu et al. state: "selection pressure may be used to favor the proliferation of human hepatocytes. Such selection pressure is defined herein as including any condition, preexisting in the host animal at the time of introduction of donor cells or imposed thereafter, which results in a greater likelihood that human hepatocytes, rather than host hepatocytes, will proliferate. For example, the selection pressure may result from the presence of a transgene that decreases the viability of host hepatocytes, either intrinsically (directly) or by administration of an activating agent (indirectly)... the transgene may be the albumin promoter/HSV-TK construct, whereby when gancyclovir is administered to the host animal (e.g., as an intraperitoneal injection of 250 mg/kg gancyclovir in sterile PBS), hepatocytes of the transgenic host may be selectively killed. In such embodiments, the death of host hepatocytes would be expected to favor compensatory proliferation of human hepatocytes." (column 18, lines 20-48). Thus, the human foreign replacement cells replace destroyed cells of the liver tissue (limitation of claim 1).

Therefore by teaching all the limitations of claims 1, 2, 4, 5, 7 and 8, Wu et al. anticipate the instant invention as claimed.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 3 are rejected under 35 U.S.C. §103(a) as being unpatentable over Wu et al. (U.S. Patent No.: 6,995,299; filed Aug. 15, 2001), in view of Loeb et al. (U.S. Patent No: 6,451,571; filed Sep. 17, 2002).

Wu et al. describe propagation of human hepatocytes in non-human animals, wherein said animals have chimeric livers, whereby some of substantially all of the hepatocytes present are human hepatocytes (Title and Abstract), and wherein the animal comprising human hepatocytes is preferably a fetus (column 5, line 5). Wu et al. additionally describe the host animal as a transgenic animal carrying, as a transgene, a gene which, when expressed in hepatocytes, is indirectly (i.e. via a metabolite) toxic to those cells and provide the Herpes simplex virus ("HSV") thymidine kinase gene ("HSV-TK") as one example (columns 12 and 13, bridging).

While Wu et al. do not describe the TK gene as a mutated thymidine kinase, Loeb et al. describe various thymidine kinase mutants having increased biological activity compared to unmutated thymidine kinase (Abstract). Gregory et al. additionally state that the thymidine kinase mutants may be expressed in non-human transgenic animals such as sheep and pigs (column 15; lines 19-21).

Thus, Loeb et al. cure the deficiency in Wu et al. for a mutated thymidine kinase, and further provide the motivation to substitute mutated thymidine kinase for the wild type form, as the mutated form has increased biological activity.

Therefore, a person of ordinary skill in the art would have been motivated to combine the teachings of Wu et al. and Loeb et al. and include a mutated thymidine kinase in place of a non-mutated form to selectively destroy native host cells, as instantly claimed, with a reasonable expectation of success, because the mutated thymidine kinase would be more effective at cellular ablation, requiring lower expression of the transgene and prodrug to be administered.

Thus it would have been *prima facie* obvious for a person of ordinary skill in the art, to include a mutated thymidine kinase, as a transgene for expression in fetal cells of a artiodactyls host, at the time of the instant invention.

Claims 1 and 9-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wu et al. (U.S. Patent No.: 6,995,299; filed Aug. 15, 2001), in view of Sorscher et al. (U.S. Patent No.: 6,017,896; filed Jun. 24, 1997).

Wu et al. describe propagation of human hepatocytes in non-human animals, wherein said animals have chimeric livers, whereby some of substantially all of the hepatocytes present are human hepatocytes (Title and Abstract), and wherein the animal comprising human hepatocytes is preferably a fetus (column 5, line 5). Wu et al. additionally describe the host animal as a transgenic animal carrying, as a transgene, a gene which, when expressed in hepatocytes, is indirectly (i.e. via a metabolite) toxic to those cells and provide the Herpes simplex virus ("HSV") thymidine kinase gene ("HSV-TK") as one example (columns 12 and 13, bridging).

While Wu et al. do not describe the use of immunoliposomes to specifically target and deliver the prodrug for their TK toxin gene, Sorscher et al. describe a method of killing replicating or non-replicating mammalian cells transduced with a nucleic acid encoding non-human purine cleavage enzyme and contacting the transduced cells with a substrate for the enzyme, wherein the substrate is non-toxic to mammalian cells, and is cleaved by the enzyme to yield a product toxic to the targeted mammalian cells to kill the mammalian cells expressing the enzyme (Abstract). Additionally teaching the targeting of liposomes to specific sites by the inclusion of specific ligands or antibodies in their exterior surface, in which specific liver cell populations are targeted by the inclusion of asialofetuin in the liposomal surface, further teaching that the strategy of targeting can be extended to specific delivery of the prodrug (column 17, lines 24-25; limitation of claims 10 and12). Thus further teaching the use of immunoliposomes and tissue-specific targeting ligands for prodrug or toxin delivery (limitation of claim 9 and 10). Thus, Sorscher et al. cure the deficiency of immunoliposome mediated tissue-specific prodrug delivery in Wu et al. and Gregory et al.

Therefore, a person of ordinary skill in the art would have been motivated to combine the teachings of Wu et al. Sorscher et al. to specifically target a prodrug to liver cells to induce selective cell killing, as instantly claimed, with a reasonable expectation of success, as a matter of design choice in situations where transgene expression in the recipient is not restricted to a specific tissue type.

Thus it would have been *prima facie* obvious for a person of ordinary skill in the art, to utilize an immunoliposome mediated delivery method to specifically target liver cells, at the time of the instant invention.

***Conclusion***

**Claims 1-5 and 7-12 are not allowed.**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fereydoun G. Sajjadi whose telephone number is (571) 272-3311. The examiner can normally be reached on 7:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Examiner, A.U. 1633

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